

## **Performance of the 2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus in Early Disease, Across Sexes and Ethnicities**

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## **Abstract**

**Objectives.** The EULAR/ACR 2019 Classification Criteria for systemic lupus erythematosus (SLE) have been validated with high sensitivity and specificity. We evaluated the performance of the new criteria with regard to disease duration, sex, and race/ethnicity, and compared its performance against the SLICC 2012 and ACR 1982/1997 criteria.

**Methods.** Twenty-one SLE centers from 16 countries submitted SLE cases and mimicking controls to form the validation cohort. The sensitivity and specificity of the EULAR/ACR 2019, SLICC 2012 and ACR 1982/1997 criteria were evaluated.

**Results.** The cohort consisted of female (n=1098), male (n=172), Asian (n=118), Black (n=68), Hispanic (n=124) and White (n=941) patients; with an SLE duration of 1-<3 years (n=196) and 5 years (n=879). Among patients with 1-<3 years disease duration, the EULAR/ACR criteria had better sensitivity than the ACR criteria (97% versus 81%). The EULAR/ACR criteria performed well in men (sensitivity 93%, specificity 96%) and women (sensitivity 97%, specificity 94%). Among women, the EULAR/ACR criteria had better sensitivity than the ACR criteria (97% versus 83%) and better specificity than the SLICC criteria (94% versus 82%). Among White patients, the EULAR/ACR criteria had better sensitivity than the ACR criteria (95% versus 83%) and better specificity than the SLICC criteria (94% versus 83%). The EULAR/ACR criteria performed well among Black patients (sensitivity of 98%, specificity 100%), and had better sensitivity than the ACR criteria among Hispanic patients (100% versus 86%) and Asian patients (97% versus 77%).

**Conclusions.** The EULAR/ACR 2019 criteria perform well among patients with early disease, men, women, White, Black, Hispanic and Asian patients. These criteria have superior sensitivity than the ACR criteria and/or superior specificity than the SLICC criteria across many subgroups.

## INTRODUCTION

Classification criteria constitute a cornerstone of clinical research in Rheumatology as they facilitate identification of homogeneous groups of patients for inclusion into observational studies and clinical trials.[1] The European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) 2019 classification criteria for SLE were developed through an international collaboration using both data-driven and expert-based consensus-finding methods.[2-10] The new criteria define the presence of one or more results for antinuclear antibody (ANA) tests at a titer of  $\geq 1:80$  (or an equivalent positive test) as an entry requirement. The subsequent criteria are grouped into seven clinical domains (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal and renal) and 3 immunologic domains (antiphospholipid antibodies, hypocomplementemia, SLE-specific antibodies). Related organ system criteria are clustered hierarchically and numerically weighted to form an additive point system. A patient can be classified as having SLE if the ANA entry criterion is fulfilled, at least one clinical criterion is present, and the accumulated points of all domains total 10 or more. One attribution rule for all items replaced exclusion criteria, stating that items should only be counted if there was no explanation more likely than SLE. Novel features of the classification system are the inclusion of fever, in the absence of infection or other causes, as a criterion to assist in classification of earlier disease; and separation of class II and V from class III and IV lupus nephritis as distinct criteria. Class III or IV lupus nephritis was found to be more influential in the classification of an ANA positive individual and given 10 points, thereby forming the only singular sufficient criterion for classification of SLE in the presence of ANA.

In the validation cohort, the new criteria had a sensitivity of 96% and a specificity of 93%. This led to the endorsement of the new criteria by both EULAR and ACR.[11, 12] Through the criteria development and review processes, investigators and reviewers questioned the operating characteristics of the new criteria in subsets of SLE patients.[13] Indeed, there is a need for criteria that perform well in early disease for more timely inclusion in clinical trials and research studies.[14] Furthermore, differences in SLE disease expression have been described between sexes and across ethnicities which may impact the performance of classification criteria in these

groups of patients.[15-17] Therefore, the objectives of this study were to evaluate the sensitivity and specificity of the EULAR/ACR 2019 classification criteria in early disease, across sexes and ethnicities.[11, 12] We also comparatively evaluated the operating characteristics of the EULAR/ACR 2019 classification criteria against the ACR 1982/1997[18, 19] and the Systemic Lupus International Collaborating Clinics (SLICC) 2012[20] classification criteria for SLE.

## **METHODS**

**SLE cases and controls.** Twenty-one SLE expert centers from 16 countries submitted between 20 and 100 SLE cases and the same number of SLE mimicking controls each to form the validation cohort for the EULAR/ACR 2019 classification criteria. The investigators from these centers had not been part of the steering committee, the nominal group technique[7] nor the multicriteria decision analysis[10] of the project and were thus unaware of the new criteria form or content. The 100 case and control limit per center was used to preclude any one center from dominating the cohort. Data on all cases and controls, including demographic data and SLE duration, were collected using a standardized form.

**Data administration.** Cases and control diagnoses (SLE or not SLE) were made by the submitting investigator and were independently verified by 3 SLE experts. Previous sets of classification criteria were not considered when selecting cases nor controls. Data were double entered into a computerized database. Data quality was maintained using logic and range checks. Data queries were reconciled by interrogation of the submitting investigator. Research ethics board approval and patient consent was obtained by the data coordinating center and all submitting centers, as required locally.

**SLE subsets.** Disease duration was calculated from date of physician diagnosis to date of data submission. Data on sex were self-reported as male or female. Data on gender were not collected. Data on ethnicity, self-reported and verified by the investigators, were collected from the medical records, and categorized as White, Black, Hispanic (Latin American heritage) and Asian.



**Statistical analysis.** Sensitivity and specificity for each of the classification criteria sets among subsets of SLE patients were estimated with their corresponding 95% confidence intervals (CI). Non-overlapping confidence intervals denotes statistically significant differences. Statistical analyses were performed using R, version 3.4.0 (The R Foundation of Statistical Computing).

## RESULTS

**Cohort.** Cases and controls were submitted from centers in Austria, Canada, Croatia, France, Germany, Greece, Hong Kong, Hungary, Japan, Italy, Mexico, Portugal, Spain, Turkey, United Kingdom, and United States of America. The validation cohort (n=1270) consisted of female (n=1,098 (86%)) and male (n=172 (14%)) patients; Asian (n=118 (9%)), Black (n=68 (5%)), Hispanic (n=124 (10%)) and White (n=941 (74%)) patients; and patients with an SLE duration of less than 1 year (n=34 (3%)), 1 to less than 3 years (n=196 (16%)), 3 to less than 5 years (n=157 (12%)), and 5 or more years (n=879 (69%)). The 5 subjects who were Arab and 13 subjects who had an ethnicity categorized as 'Other' were excluded from the ethnicity analyses as their numbers were so small. Four subjects had missing disease duration data.

**Operating characteristics.** As shown in Table 1, which includes 95% CIs, the EULAR/ACR 2019 criteria performed well among patients with early disease defined as 1 to less than 3 years of disease duration (sensitivity 97%, specificity 96%) and among patients with 3 to less than 5 years disease duration (sensitivity 96%, specificity 99%). The EULAR/ACR 2019 criteria also performed well among patients with established disease defined as 5 or more years disease duration (sensitivity 96%, specificity 93%). They also perform well in men (sensitivity 93%, specificity 96%), women (sensitivity 97%, specificity 94%), and in all the race/ethnicity groups examined. Table 1.

Among women, the EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria (97% (95%CI 95-98%) versus 83% (95%CI 80-86%) and better specificity than the SLICC criteria (94% (95%CI 91-96%) versus 82% (95%CI 79-86%). (Figure 1.)

Among White patients, the EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria (95% (95%CI 93-97%) versus 83% (95%CI 79-86%) and better specificity than the SLICC criteria (94% (95%CI 91-96%) versus 83% (95%CI 80-87%). (Figure 2.) The EULAR/ACR 2019 criteria performed well among Black patients with a sensitivity of 98% (95%CI 90-100%) and specificity 100% (95%CI 74-100%). The 95% confidence intervals around these estimates are larger due to the smaller sample size. The EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria among Hispanic patients (100% (95%CI 95-100%) versus 86% (95%CI 76-93%) and Asian patients (97% (95%CI 91-100%) versus 77% (95%CI 65-86%).

In patients with 1 to less than 3 years disease duration, the EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria (97% (95%CI 92-99%) versus 81% (95%CI 72-88%). Among patients with 5 or more years disease duration, the EULAR/ACR 2019 criteria had better sensitivity than the ACR 1982/1997 criteria (96% (95%CI 94-98%) versus 84% (95%CI 80-87%) and better specificity than the SLICC criteria (93% (95%CI 89-95%) versus 81% (95%CI 76-85%). Among SLE patients with less than 3 years disease duration (early disease), oral ulceration, non-scarring alopecia and pleural/pericardial effusions occurred more frequently. Among SLE patients with a disease duration of 5 or more years, acute cutaneous lupus, arthritis, seizures, pericarditis, leukopenia and class III or IV nephritis occurred more frequently. Table 3.

The operating characteristics of the ACR 1982/1997 and SLICC 2012 reported in other studies are summarized in Table 2 and are generally consistent with their performance in the present study.

## **DISCUSSION**

The EULAR/ACR 2019 criteria have strong operating characteristics (sensitivity and specificity) across subsets of SLE patients, specifically among male and female, White, Black, Hispanic and Asian patients. Importantly, the new criteria perform well among patients with early disease. Indeed, this was one of the reasons to develop new classification criteria. Furthermore, the new criteria confer improved performance compared to previous sets of SLE classification criteria, retaining their superior sensitivity compared to the ACR criteria, as well as their superior specificity compared to the SLICC criteria in many of these groups. There was no subset of patients identified in which the new criteria performed substantially worse than previous criteria. The EULAR/ACR 2019 SLE criteria reflect the current thinking of the international SLE community about how SLE is to be classified and reduce the potential risk of misclassification of ANA positive patients.

Our demonstration that the EULAR/ACR 2019 SLE criteria perform well in early disease is an important contribution to the field. We tested different definitions of early disease (less than 1 year, 1 to less than 3 years, 3 to less than 5 years disease duration), and in all of our definitions, the new criteria performed well. The validity of classification criteria for early disease allows for more timely inclusion in clinical trials and observational studies. It is hoped that intervention in those early in their disease course may prevent complications and irreversible damage.[14] Identifying when the disease started can be challenging as a patients may have symptoms or even full SLE for a period of time before being diagnosed. We note that there is no standardized definition of 'early' SLE. However, other definitions of early, very early, latent or incomplete disease (i.e. other terms used to describe patients with some symptoms and signs of SLE) have been proposed.[14, 21] In this study, disease duration was calculated from the date of physician diagnosis to date of data submission. While such data are not available from the EULAR/ACR patient data set, another very important stage of the disease is from first sign or symptom to diagnosis. We encourage investigators to test the performance of the new classification criteria using these alternative definitions of 'early' disease. It should be noted, that in our study, the diagnosis of all cases and controls was verified by 3 independent reviewers from different centers, thereby reducing potential bias of a submitting center. If investigators test alternative

definitions of early disease, we encourage investigators to submit cases and controls for independent verification.

The operating characteristics of the ACR 1982/1997 and SLICC 2012 criteria in this study were similar to those reported by others.[22, 23] Among Asian patients, Oku et al reported sensitivity and specificity of the ACR criteria (88% and 85%, respectively) and the SLICC criteria (99% and 80%, respectively).[24] Among patients with less than 5 years disease duration in the Portuguese and Spanish National Registries (Reuma.pt and RELESSER cohorts, respectively), Ines et al reported a sensitivity of 76% for the ACR criteria and 89% for the SLICC criteria.[23] Similarly among patients with >5 years disease duration, they reported a sensitivity of 89% for the ACR criteria and 90% for the SLICC criteria.[23] In an international early SLE cohort, Mosca et al reported similar sensitivity and specificity as Ines et al for the ACR criteria (66% and 97%, respectively) and the SLICC criteria (84% and 82%, respectively).[5] Thus, the performance characteristics of previous iterations of SLE classification criteria in our study are similar to those in other cohorts and therefore further support the generalizability of our conclusions.

One potential limitation of this study is the numbers of patients from non-White ethnicities. Although we had sufficient numbers of patients to estimate performance in multiple subgroups, larger numbers of patients would improve the precision of our estimates. This is particularly true of the Black patient subset. The underrepresentation of Black patients in this cohort may be partially explained by a low number of Black patients in European cohorts. It may also reflect a sampling bias that occurred by chance in the North American cohorts. There is a need for more Black patients with SLE and control group diseases to refine the precision of our estimates evaluating the operating characteristics of the new criteria in this group. Moreover, there were only three centers from Asia and none from Africa or South America contributing patients to this analysis. Future collaborative studies by EULAR and ACR should consider recruiting a broader spectrum of referral centers from these regions to avoid similar

limitations. Investigators are encouraged to test these new criteria in larger numbers of Black patients and other race/ethnic groups as well as SLE centers worldwide.

Secondly, these subgroup analyses were conducted using the same cohort to validate the new criteria. The observed excellent operating characteristics across subgroups is similar in magnitude to the operating characteristics observed in the whole cohort. Others are encouraged to test the performance characteristics in independent cohorts.[25] Two cautionary notes are made to investigators who embark on comparative evaluation of the new criteria to previous classification criteria. The new classification criteria are not diagnostic criteria. Neither EULAR nor ACR endorse the development or validation of diagnostic criteria. [26] It is therefore inappropriate to evaluate these criteria as diagnostic criteria.[26] These criteria have been endorsed for identifying SLE patients for research studies and will facilitate comparisons across studies. The diagnosis of SLE remains in the domain of the appropriately trained physician. These criteria should have no treatment implications for patients.[26] Most importantly, failure to fulfil these criteria should not be used by payers to deny appropriate therapy to patients, which in the case of the EULAR/ACR criteria prominently applies to patients who never had positive ANA.

A critical feature of the reliable application of these classification criteria is appropriate attribution. A criterion should not be counted if there is a more likely explanation than SLE. The requirements to use the precise definition of criteria and ascertain correct attribution for each criterion may reduce the opportunity of testing the criteria performance in pre-existing databases. These requirements are necessary for achieving specificity and facilitating reliable application of the criteria between sites and between studies.

In conclusion, the EULAR/ACR 2019 SLE classification criteria perform well among patients with early disease. The new SLE classification criteria also perform well in both sexes, and among White, Black, Hispanic and Asian patients. More work is needed to improve the precision of the estimates among Black and evaluate criteria performance in other race/ethnicities. Overall, the

new criteria provide added value compared to previous versions of SLE classification. The EULAR/ACR 2019 SLE criteria provide early and accurate classification of SLE across various SLE patient subpopulations.

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**Table 1.** Sensitivity and Specificity of SLE Classification Criteria Across Sexes, Ethnicities and Disease Duration

	Sensitivity 95% CI			Specificity 95% CI		
	ACR 1982/1997 Criteria	SLICC 2012 Criteria	EULAR/ACR 2019 Criteria	ACR 1982/1997 Criteria	SLICC 2012 Criteria	EULAR/ACR 2019 Criteria
<b>Sex</b>						
<b>Women</b>	<b>0.83</b>	<b>0.97</b>	<b>0.97</b>	<b>0.93</b>	<b>0.82</b>	<b>0.94</b>
n=1,098	0.80-0.86	0.95-0.98	0.95-0.98	0.91-0.95	0.79-0.86	0.91-0.96
<b>Men</b>	<b>0.78</b>	<b>0.94</b>	<b>0.93</b>	<b>0.94</b>	<b>0.9</b>	<b>0.96</b>
n=172	0.68-0.87	0.87-0.98	0.86-0.98	0.87-0.98	0.82-0.96	0.90-0.99
<b>Disease Duration</b>						
<b>&lt; 1 year</b>	<b>0.56</b>	<b>0.89</b>	<b>0.89</b>	<b>0.92</b>	<b>0.92</b>	<b>0.92</b>
n=34	0.21-0.86	0.52-0.99	0.52-1.00	0.74-0.99	0.74-0.99	0.74-0.99
<b>1 to &lt;3 years</b>	<b>0.81</b>	<b>0.98</b>	<b>0.97</b>	<b>0.95</b>	<b>0.88</b>	<b>0.96</b>
n=196	0.72-0.88	0.93-1.00	0.92-0.99	0.88-0.98	0.80-0.94	0.90-0.99
<b>3 to &lt;5 years</b>	<b>0.81</b>	<b>0.91</b>	<b>0.96</b>	<b>0.94</b>	<b>0.89</b>	<b>0.99</b>
n=157	0.70-0.90	0.82-0.97	0.88-0.99	0.87-0.98	0.80-0.94	0.94-1.00
<b>≥5 years</b>	<b>0.84</b>	<b>0.97</b>	<b>0.96</b>	<b>0.93</b>	<b>0.81</b>	<b>0.93</b>
n=879	0.80-0.87	0.96-0.99	0.94-0.98	0.90-0.95	0.76-0.85	0.89-0.95
<b>Ethnicity</b>						
<b>White</b>	<b>0.83</b>	<b>0.96</b>	<b>0.95</b>	<b>0.93</b>	<b>0.83</b>	<b>0.94</b>
n=941	0.79-0.86	0.94-0.97	0.93-0.97	0.90-0.95	0.80-0.87	0.91-0.96
<b>Black</b>	<b>0.82</b>	<b>0.98</b>	<b>0.98</b>	<b>1</b>	<b>0.92</b>	<b>1</b>
n=68	0.70-0.91	0.90-1.00	0.90-1.00	0.74-1.00	0.62-1.0	0.74-1.00
<b>Hispanic</b>	<b>0.86</b>	<b>1</b>	<b>1</b>	<b>0.96</b>	<b>0.78</b>	<b>0.96</b>
n=124	0.76-0.93	0.95-1.00	0.95-1.00	0.87-1.00	0.65-0.89	0.87-1.00
<b>Asian</b>	<b>0.77</b>	<b>0.99</b>	<b>0.97</b>	<b>0.93</b>	<b>0.91</b>	<b>0.91</b>
n=118	0.65-0.86	0.93-1.00	0.91-1.00	0.82-0.99	0.79-0.98	0.79-0.98

ACR American College of Rheumatology, SLICC Systemic Lupus International Collaborating Clinics, EULAR European League Against Rheumatism

Non-overlapping confidence intervals indicates statistical significance

**Table 2.** Summary of previously published operating characteristics of SLE classification criteria among patient subsets

Reference	Subset	ACR Criteria		SLICC Criteria	
		Sensitivity % (95%CI)	Specificity % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)
Ethnicity					
Oku et al. 2018	Asian	88% (83 - 92%)	85% (80 - 89%)	99% (96 - 100%)	80% (75 - 85%)
Disease duration					
Ighe et al. 2015	0 – 4 years	ACR 1982 60% (44 - 75%)	NR	89% (73- 97%)	NR
	5 – 9 years	89% (77 - 96%)	NR	89% (77 - 96%)	NR
	10 – 14 years	76% (62 - 86%)	NR	88 % (75 - 95%)	NR
	15 – 19 years	69% (54 - 81%)	NR	84% (71 - 93%)	NR
	≥20 years	86% (75 - 92%)	NR	97% (89 - 100%)	NR
Ighe et al. 2015	0 – 4 years	ACR 1997 82% (65 - 92%)	NR	SLICC* 80% (64 - 91%)	NR
	5 – 9 years	94% (84 - 99%)	NR	84% (71 - 92%)	NR
	10 – 14 years	91% (79 - 98%)	NR	84% (70 - 92%)	NR
	15 – 19 years	86% (72 - 94%)	NR	80% (66 - 90%)	NR
	≥20 years	91 % (82 - 97%)	NR	94% (85 - 98%)	NR
Ines et al. 2015	Any duration	ACR 1997 86%	NR	93%	NR
	≤5 years	76%	NR	89%	NR
	>5 to ≤10 years	82%	NR	90%	NR
	>10 to ≤15 years	88%	NR	95%	NR
	>20 years	94%	NR	97%	NR
Mosca et al. 2019	Early cohort, At diagnosis	66%	92%	84%	82%

\*SLICC-12 with a requirement for involvement of at least two organ systems for SLE diagnosis  
NR Not reported

**Table 3.** Frequency of criteria in early and established SLE

<b>Criteria</b>	<b>Early Disease &lt;3 years duration</b>	<b>Established disease &gt;5 years duration</b>
<b>Constitutional</b> Fever	12.6%	15.1%

<b>Mucocutaneous</b>		
Non-scarring alopecia	29.4%	26.4%
Oral ulcers	25.2%	17.9%
Subacute cutaneous or discoid lupus	11.1%	11.3%
Acute cutaneous lupus	34.2%	44.5%
<b>Arthritis</b>	28.7%	69.3%
<b>Neurologic</b>		
Delirium	0%	0.6%
Psychosis	2.1%	1.4%
Seizure	2.1%	5.6%
<b>Serositis</b>		
Pleural or pericardial effusion	18.9%	10.5%
Acute pericarditis	3.5%	6.8%
<b>Hematologic</b>		
Leukopenia	39.9%	44.5%
Thrombocytopenia	41.3%	35.9%
Autoimmune hemolysis	18.9%	19.6%
<b>Renal</b>		
Proteinuria >0.5g/24h	9.8%	7.2%
Renal biopsy Class II or V lupus nephritis	7.0%	8.9%
Renal biopsy Class III or IV lupus nephritis	16.1%	24.7%
<b>Antiphospholipid antibodies</b>		
Anti-cardiolipin antibodies or Anti-β2GP1 antibodies or Lupus anticoagulant	26.6%	28.0%
<b>Complement proteins</b>		
Low C3 or low C4	21.7%	24.7%
Low C3 and low C4	49.7%	46.2%
<b>Highly specific antibodies</b>		
Anti-dsDNA antibody or Anti-Smith antibody	83.2%	78.3%

**Figure 1.** Forest plot comparing the sensitivity and specificity of SLE classification criteria in Women.

Footnote. CI 95% confidence interval. All women (n=1098) were included in this analysis

**Figure 2.** Forest plot comparing the sensitivity and specificity of SLE classification criteria in White subjects

Footnote. CI 95% confidence interval. All White subjects (n=941) were included in this analysis.



## **Key Messages**

### **What is already known about this subject?**

Classification criteria are needed to identify homogeneous groups of patients for inclusion into clinical trials and observational studies. The 2019 EULAR/ACR Classification Criteria have excellent sensitivity and specificity.

### **What does this study add?**

The 2019 EULAR/ACR criteria perform well among patients with early disease, men, women, White, Black, Hispanic and Asian patients.

### **How might this impact on clinical practice?**

These criteria have superior sensitivity than the ACR criteria and/or superior specificity than the SLICC criteria across many subgroups. They can be used as inclusion criteria for study of novel treatments in systemic lupus erythematosus.